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AND THE SCIENCES
SUPPORTING PUBLIC HEALTH

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AMERICAN JOURNAL OF PHARMACY

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EDITORIAL

RESEARCH—PURE AND APPLIED

THE importance of research is so generally accepted today that little argument is necessary to convince even the most reactionary and backward of its necessity. American industry owes much of its progress to the heavy financial support which it has given research. There are hundreds of cases of industrial failure through lack of adequate research just as there are some fantastic success stories resulting from the fortuitous combination of research and good luck or chance, if you prefer it. That chance is a factor cannot be denied. One has only to cite the field of antibiotic research to prove this. All of the major pharmaceutical companies have engaged in extensive antibiotic screening programs but not all were lucky enough to find a chloromycetin or an aureomycin. A single find such as either of these is sufficient to underwrite a tremendous research expenditure but such success cannot be predicted in advance. In the long run, however, research pays, and this is a well accepted fact even by financiers with no technical background. Most large companies have established a fixed policy of allocating a definite per cent of their gross profit or sales to research. As a result, we have in America some of the world's best research teams. Industrial research is such a complex matter that it requires a collection of experts. Each field of science is itself so extensive that a score or more of specialists may be required just for this field alone. The modern research team is a carefully coordinated and integrated group of specialists each adhering pretty closely to his specialty but working together under efficient direction and administration. The importance and recognition of such teamwork was given a great impetus by the phenomenal success of this type of organization during World War II. Without such a closely knit team the atomic bomb could not have been produced, at least not in the record time that it was done.

The great problem today is the lack of support, financial and otherwise, given to pure research—research not intended to provide some immediate product or gadget that has sales potential but one which is solely for the purpose of extending the frontiers of human knowledge. Only the most philanthropic of industrialists are willing to allocate funds for this type of work and thus educational institutions and government laboratories carry the greatest burden of such re-

search activities and far too little is being done. It is not a simple matter to "sell" the typical American businessman on the need for supporting extensive research where there appears not the slightest chance of some practical application. At one time this was not too serious since the scientist who wished to study some problem in which he was interested required only the most inexpensive apparatus and equipment. Today, little can be done without equipment which is very expensive since as the frontier of human knowledge has been pushed out, nature yields her secrets only with more and more effort and ingenuity. There is a great difference in cost, as well as in what can be done, when one compares a test tube with an infra-red spectrophotometer or a beaker with a cyclotron.

Pure research is actually the source of all our present technology and material achievement. Back of every profitable or worthwhile product made and sold by industry lies a long list of published data carefully collected by quiet men working in their laboratories, often unnoticed and without acclaim or recognition during their entire lifetime. Society owes far more than is realized to these men and women who chose an unglamorous and unprofitable career because they at heart were true scientists and asked nothing better of life than the privilege of studying some phenomenon which excited them more than fame or riches. These come later, as a rule, to those who exploit the true scientist's achievements.

Only too often is the humble scientist, working in obscurity, ridiculed by his more successful brothers who have sold their talents to the highest bidder. Such workers deserve more than the indulgent and patronizing manner with which they are treated for it is men such as they who have carried the torch of human knowledge which illumines the world and has made man what he is today.

The financial support of pure research like that given to the church and charitable institutions may have no direct and tangible benefits to the giver but the intangible and eventual return is incalculable. As we in America continue to amass research facilities and progress technologically let us not forget the humble scientists who today are working in some seemingly impractical and useless area. From men such as these will come the great advances of tomorrow and, who knows, some such worker may even now be recording some data which when integrated will alter the whole course of human destiny.

L. F. Tice

Editor's Note

THIS month we are publishing some of the excellent papers presented at a symposium on "Frontiers of Research on Blood and Plasma Extenders" given on the occasion of the formal dedication of the new Sharp & Dohme Medical Research Laboratories at West Point, Pennsylvania, Monday, May 12, 1952.

It is unfortunate that space does not permit the inclusion of all of the papers, presented in each case by an outstanding authority in the specific field covered. For the benefit of our readers the following papers not included in this issue of the Journal were also presented. Arrangements may be made with the Editor should our readers wish to have the opportunity of reading them.

Studies of the Effects of Modified Human Globin in Man by Charles S. Davidson, M. D.

Recent Advances in the Preparation of Stable Plasma Derivatives by Douglas M. Surgenor, Ph. D.

Clinical Status of Dextran, PVP, and Gelatin Products by Lt. Col. Edwin J. Pulaski (MC) U. S. Army.

PROGRESS THROUGH RESEARCH *

By John S. Zinsser **

THE dedication of the new Medical Research Laboratories here at West Point, Pennsylvania, is a proud moment for Sharp & Dohme. It marks an important milestone in the history of the Company and is especially gratifying when one realizes that in 1930—just 22 years ago—Sharp & Dohme had only three full-time research scientists. Today we have a staff of over 200 men and women, more than 70 per cent of whom are scientific personnel actively engaged in the search for new and improved products for the Nation's health.

The larger part of this rapid expansion of our research activities has taken place in the last decade. It was only 10 years ago—in 1942—that we marked the official opening of our first laboratories built specifically for research. At that time, we believed that those laboratories at Glenolden, Pa., would be adequate for some years to come. But 1942 ushered in a decade in which Sharp & Dohme tripled its sales, and the Research Division increased its personnel and projects more than sixfold. The Glenolden laboratories were outgrown in less than 10 years and our research operations were scattered among 11 different buildings at our Glenolden plant.

This new, larger building once again integrates our research facilities and is symbolic of our conviction that research is the foundation upon which the health and growth of this Company depends. It is the building stone of our future. In it we hope to continue an intensified research program which now covers virtually every field of medicine.

The new laboratories were built at a cost of close to $4,000,000 and contain the most modern equipment—apparatus, instruments and machines—that are obtainable. But far more important, we believe we have an outstanding team of men and women scientists, and we are confident that they will continue the progress they have made in the past. Some of their significant accomplishments include the development of a large number of sulfa drugs in common use today,

* Delivered on the occasion of the formal dedication of the new Sharp & Dohme Medical Research Laboratories, West Point, Pennsylvania, Monday, May 12, 1952.

** Chairman of the Board, Sharp & Dohme, Incorporated.

and the development of the lyophilization technique for the processing of dried human blood plasma, which saved countless thousands of lives of wounded soldiers in World War II, and is doing the same work today in Korea.

Sharp & Dohme scientists have many more less dramatic achievements to their credit. The fact that considerably more than half of our current sales are in new and improved products introduced in the last 10 years—and our sales have tripled—is sufficient testimony to the kind of work they are doing.

This growth through progress in research has also meant more jobs for more people. In 1942, Sharp & Dohme had 2,500 people on its payrolls. Today, the Company employs approximately 3,700 men and women, who serve the medical and allied professions in all parts of the world. So it is not difficult to demonstrate that research and industrial progress go hand in hand, and that this partnership makes for economic strength. And economic strength is the bulwark of security.

In addition to the Research Division, the Medical and Patent Divisions make their headquarters in the new building. Our physicians in the Medical Division have the important job of introducing to clinical investigators, for careful trial in humans, promising new products that have passed long and rigid tests in our laboratories. Only after long and extensive studies by clinical investigators in hospitals, clinics and medical centers across the country, to assure the safety and efficacy of a new product in humans, does Sharp & Dohme or any company in the drug industry attempting to get permission to market a new product for general use from the Food and Drug Administration, National Institutes of Health, or the Bureau of Animal Industry. These are governmental agencies which have the responsibility of passing on or rejecting applications for the commercial sale of health products.

The Patent Division, of course, is responsible for obtaining patents on inventions by Company scientists and engineers and trademarks for new products. Our patent attorneys also make certain that Sharp & Dohme does not infringe upon the patents or trademarks of other companies and protects Sharp & Dohme from infringement by others on our patents and trademarks.

Research in the drug industry, as in most progressive industries in the United States today, is highly competitive, but it is the very

nature of this competition that has made for such rapid strides in the development of new and better products for the treatment and prevention of disease. It has brought untold benefits to the sick and suffering the world over, and the accomplishments of our country's medical research scientists are a tribute to the system of free competitive enterprise under which they operate.

Such competitive research demands an aggressive spirit in which each new development of a competitor must be looked upon as a challenge to be met and bettered. It requires men and money to stay in the game. We are spending large sums in this work.

Research on such a scale involves risk taking—projects on which large amounts of money are expended are not always successful. We believe this investment is an expression of our faith in the future. And the most important element in that future is the preservation of freedom that has given this country the highest standard of living the world has ever known.

I am deeply honored to participate with the distinguished group of medical authorities who are represented on the symposium panel to follow. May I take this opportunity to thank them personally for joining with us today in dedicating the new Sharp & Dohme Medical Research Laboratories to the service of the medical and allied professions and the nation's health.

NEWER METHODS OF BLOOD COLLECTION

By Carl W. Walter, M. D.*

THE purpose of a technical procedure is often lost in the hysterical joy of inventing equipment and elaborating technic. This is particularly true of a procedure that has challenged man's creative imagination for four centuries.

In 1840, Richard Oliver penned a classic description of the purpose of today's symposium.

> "Blanched by profuse hemorrhage, which no adequate means had been employed to suppress, but which had now ceased, she was lying on her back in a state of imperfect consciousness, with the pulse at her wrist barely perceptible . . . deceitful promises of reaction were succeeded by progressive indications of sinking . . . I was provided with the apparatus necessary for performing transfusion; and having obtained a willing supply of blood from three of the patient's kind-hearted neighbors, I opened a vein at the bend of the elbow . . . we had the very perfect gratification of witnessing not only the complete restoration of the circulatory powers, but the return of consciousness."

It is obvious that Oliver transfused enough fresh blood to substitute for that lost by profuse hemorrhage. It is paradoxical that a century of progress in technic has improved the availability and quantity rather than the quality of blood used for substitution therapy.

The fresh blood transfused by Oliver differed markedly from the blood infused into almost all patients today. Current knowledge tells us that the cells in his blood were a living population with normal life expectancy. All old, degenerated cells had been scavenged by the donor's reticuloendothelial system. The erythrocytes, platelets and leukocytes present in the blood retained functional capacity, and effectively restored the red cell mass and bolstered the clotting mechanism.

About one per cent of the donor's cells died of old age daily and were scavenged. The youngest of the infused cells disappeared from the recipient's circulation 100-120 days after transfusion.

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* Assistant Clinical Professor of Surgery, Harvard Medical School.

Contrast this with blood supplied by modern blood bank technic. Senescence of red cells proceeds in the refrigerator at the same rate as *in vivo*. As the population ages, an increasing percentage of red cells irreversibly deteriorates. When the blood is infused, both viable cells and the superannuated cells find their way into the patient's circulation. The latter are removed from the circulation rapidly, even during infusion.

The freed hemoglobin may be a distinct liability to the patient with peripheral vasoconstriction and renal ischemia. To others, the deficit in viable red cells may cause five infusions to be given to accomplish the repair usually expected after three transfusions of fresh blood.

Platelets live for six days under usual circumstances. Obviously under blood bank conditions, the majority are gone while the lab work is being done.

Blood degradates in other ways too complex for consideration here. The able clinician will therefore choose his blood collecting technic to fit his patient's need rather than to suit the convenience of a blood program. Four kinds of blood are available to satisfy distinct clinical needs.

The first of these is whole blood taken from the recipient and infused into the patient with minimal delay. Modern technic of blood collection removes the factor of common site and time of collection and infusion. A good hemo repellent system permits the blood to be collected through a suitable phlebotomy needle into plastic bags for subsequent infusion without the use of anti-coagulant. Periods up to six hours have elapsed between collection and infusion without clotting. This type of blood has proven useful in hemorrhage during obstetrical procedures, in blood dyscrasias and following the hemorrhagic type of transfusion reaction. A donation of blood from an erythremic donor is often spectacular in the treatment of the latter problems.

The second type of blood is decalcified blood collected through a cation exchange column. It has proven particularly useful as a starting point for plasma fractionation, for loading artificial heart-lung apparatus, in many hemorrhagic problems, and in cases where low sodium and potassium content are important as in certain postoperative states and nephrosis. When collected into dextrose, the storage period for optimum viability is four to five days.

The third type of blood is collected in the commonly used ACD anticoagulant and nutrient solution. It should be used as fresh as possible although its infusion is safe and effective for three-quarters of transfusion problems up to 25 days and under emergency conditions for 30 days. Old blood should be avoided particularly in severe shock, burns, crush injuries and when multiple infusions are contemplated because the free hemoglobin may damage ischemic renal tissue.

The fourth type of blood consists of resuspended red cells. This permits maximal additions to the patient's red cell mass with but half the fluid volume, minimal increase in oncotic power and elimination of 75 per cent of the sodium content of whole blood. Patients with low cardiac reserve, chronic anemia and the nephridites benefit from this technic.

The plastic equipment has been designed to meet these clinical needs for collection. It also provides storage and infusion of blood, protection for the donor, ensures maintenance of asepsis, increases the stability of the blood and makes infusion more effective.

Syncope with its apprehension, perspiration, nausea and often prolonged weakness is a major deterrent to many donors. Slow withdrawal of blood permits compensation for the change in blood volume due to phlebotomy and donor reactions are minimal. The fact that the bladder contains only liquid is positive assurance that air embolism, a real hazard recognized by experienced phlebotomists, can not occur.

The equipment for the ACD technic consists of a laminar flow phlebotomy needle, an integral donor tube and a collapsible bag of polyvinyl resin so designed that the unit is sterilized, assembled and filled, ready for use, by exposure to saturated steam at 121°C. for 30 minutes.

Phlebotomy is accomplished with a specially ground and polished stainless steel cannula that flares to meet the wall of the donor tube to preserve laminar flow and thus prevent platelet aggregation. An adherent, hemo-repellent film of tris-(2-hydroxyethyl)-dodecyl amine * is applied to the needle to delay the initiation of clot formation. Blood will flow continuously for over two hours impelled by venous pressure alone at the rate of 17 cc. per minute through such a needle lying in an antecubital vein.

* The Armour Laboratories, Chicago.

The polyvinyl resin is chemically inert to biologic fluids and is non-irritating to tissue. Its glossy surface is hemo-repellent. Tubing made of it is elastic and flexible enough so that a needle lying in a vein will determine the position of the tubing even though there is limited motion of the vein. The plastic is clear, colorless and transparent so that the provision of viewing chambers is unnecessary. A film of this plastic can be heat sealed. It is a bacterial barrier and transmits water vapor at the rate of 0.025 mg. per sq. cm. per 24 hours at 20°C. but is not an osmotic membrane.

The blood is collected, stored and administered in a collapsible bladder having an integral donor tube.

The blood or those fractions separable by gravity are removed from the bag through suitable delivery tubes that are closed by a diaphragm that forms a barrier across the tubes. The outer ends of the tubes are enclosed in a pouch to prevent bacterial contamination.

The technic for using the bags is simple; the donor lies supine with a pneumatic tourniquet distended to 60 mm. Hg. applied to the arm. The skin overlying the antecubital fossa is disinfected. A wheal of one per cent procaine hydrochloride is raised in the skin and the tissues about the vein are infiltrated. A loose overhand knot is formed in the mid portion of the donor tube and the bag is suspended on a spring scale with the delivery tubes uppermost. The protective sheath is removed from the phlebotomy needle. Phlebotomy is accomplished. When 640 grams have been collected, the knot is set tightly to seal the bag. The pressure is then released from the tourniquet and the needle is withdrawn from the vein.

The blood in the donor tube is sealed off in aliquots by applying R-F energy across the tubing while it is compressed in the jaws of a sealer. The final seal is made at the junction of the donor tube with the bag.

Samples of citrated blood can be preserved for cross matching by stripping the blood from the donor tube and permitting it to refill with citrated blood prior to sealing off the tube at the bag. This is done by flexing the tube over the edge of a throat stick just proximal to the knot and drawing the stick to the bag, leaving collapsed tubing distal. Serum for serology and grouping can be obtained by sealing off whole blood in the end of the tube prior to stripping the blood from the remainder. Segments of the donor tube are cut free and

centrifuged in a 15 cc. trunnion cup filled with water. An aluminum tubing clip is applied at the plasma-red cell interface and the seals are cut from either end. Individual drops of plasma or red cells can be ejected by slight pressure on the appropriate tube.

The hermetically sealed bag is suspended from a metal stand. The pilot tubes may be inserted in the identification tag fastened to the bag. The unit is refrigerated at 4°C. plus or minus one degree.

The blood is administered by pulling apart the tabs of the protective pouch about the blood delivery tube. The coupler is twisted into the lumen of the delivery tube simultaneously to penetrate the diaphragm and couple with the delivery tube.

Positive pressure infusion is readily performed by slipping the bag, with a recipient set attached, into a pneumatic press where controlled pressure is applied to force the blood out of the bag. Appropriate pressure is applied to attain the desired flow.

Plasma can be removed from the bags following either sedimentation or centrifugation. For the latter, the bag is placed in the conventional 600 cc. trunnion cup and the space about the bag is filled with water. After properly balancing the opposed cups, the cells are packed by 20 minutes exposure to 2100 x G. centrifugal force. The bag is removed from the centrifuge and placed in the pneumatic press described above. The plasma delivery tube is exposed by pulling apart the protective pouch and the diaphragm is pierced by a coupler connected by tubing to the plasma collecting container. Air is pumped into the press to force the plasma out of the bag. As the plasma-red cell interface rises into the delivery tube, a clamp is applied to effect accurate separation. By this technic, over 99 per cent of the plasma can be removed. The cells can be resuspended or washed by using the plasma delivery tube as the port for adding the appropriate solution. When resuspension is completed, the delivery tube is resealed by clamping it in the jaws of the R-F sealer and applying current for five seconds. The resuspended red cells are infused by the technic described for the administration of blood.

Logistic advantages of this equipment are many. The bag of ACD with its integral donor set weights 115 grams packaged in an aluminum tube—16 per cent of the weight of a conventional blood container. The integral donor set obviates a separate part to be procured, inventoried and distributed. The equipment can be shipped or stored in temperatures ranging from —56 to plus 76°C. As

packed commercially, four bags sealed in a tin can weigh 586 grams and occupy 1100 cc.—13 per cent of the space occupied by conventional equipment with comparable function. The bags weigh 620 grams when full of blood in contrast to 1070 grams for a full bottle. Two bags of blood can be shipped in the space occupied by one bottle. The cost of transporting plastic equipment charged with ACD to the donor center, and returning the blood to the point of origin is 25 per cent of that for glass.

The progenitor of this plastic equipment was first illustrated in Ettmuller's "Nouvelle Chirurgie" in 1691. A goose quill, treated with oil from the preen gland, tied in the neck of an inverted pig bladder served early transfusionists well.

PRESERVATION OF WHOLE BLOOD AND RED CELLS

By Robert B. Pennell, Ph. D.*

IN a majority of instances where transfusion is needed, the agent of first choice is compatible whole blood. Even when whole blood is not the most desirable agent, resuspended erythrocytes are often indicated. The development of modern blood banking technique, with its extensive understanding of blood typing, already has made both of these agents available in a manner not believed possible a few years ago. There remains, however, a single major obstacle to the fullest realization of the potentialities of these materials. That obstacle is the inability to maintain blood in a state suitable for transfusion for periods longer than about 21 days.

This is not for lack of effort to develop methods that will provide for prolonged blood storage. But, though evidence of some small progress in this field will be presented, there are as yet no really satisfactory practical techniques for a major extension of the life of blood outside of the organism. So much effort has been spent on these studies in so many laboratories that it seems desirable at this time not only to report the present status of blood storage, but also to re-examine the nature of the problem in the hope that such an examination may suggest the path to new research.

Let us first define the problem. Blood is an extremely complex tissue which, like other tissues, exists in the body in a dynamic state. We know that it consists of three major types of cellular elements, erythrocytes, leucocytes and platelets and a fluid portion, plasma, in which some 35 proteins in solution have been identified. Now plasma is known to be useful for most transfusion purposes long after it has lost many of the properties characteristic of its native state. Platelets and white cells, even when collected by the most careful methods, are probably destroyed soon after transfusion, but this destruction causes no major difficulty. These cellular elements, while vital in special instances, are not essential in most transfusions. In contrast, red cells provide the increased oxygen transport that is most

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often needed in transfusions and the rapid destruction of defunct red cells in the body causes severe clinical reactions. Thus, superficially at least, the problem of blood storage consists in keeping the predominant cellular element, the erythrocyte, in a state in which it can maintain its major function of oxygen transport.

It was stated, however, that blood exists in a dynamic state in which there are many interactions among the components. Our knowledge of these interactions insofar as erythrocytes are concerned is not yet extensive, but it is suggestive. It has been shown by Tullis that a nucleoprotein released by white cells will hasten the destruction of red cell membranes. It has been shown in our laboratory that a protein from plasma will lend increased stability to the red cell membrane. The well-known interaction of isohemaglutinins with red cells has given rise to the extensive field of blood typing. It has been reported that tagged cholesterol introduced into the blood stream is rapidly taken up by the beta-1 lipoprotein of plasma and that this cholesterol exchanges rapidly with the cholesterol of the red cell membrane. An antisphering factor present in plasma helps preserve the biconcave discoidal shape of the erythrocyte. I am suggesting that maintenance of erythrocytes in whole blood can only superficially be considered a problem to be solved by attention to the red cell alone. In the final analysis, it is unalterably interrelated with the maintenance of the other components of blood because of these, and probably of other yet unrecognized, natural interactions. It is perhaps for these reasons that the problem of storing red cells separated from other plasma components has appeared somewhat more amenable to manipulation than has the storage of whole blood.

Even though we may not legitimately concern ourselves with erythrocytes alone, it is the state of the erythrocyte that ultimately defines the suitability of blood for transfusion. Laboratory data have so frequently been misleading in forecasting *in vivo* survival of red cells that there is a tendency, where possible, to dispense with such data in blood storage studies and to go directly to the clinic. The number of variables to be manipulated is so great, however, that it would appear to be absolutely essential to do preliminary laboratory studies for selection of those techniques most likely to justify clinical study.

Some of the confusion in the determination of the status of red cells during storage may have arisen from what appear to be two

avenues of approach to the problem, nourishment of the cell and maintenance of structural integrity. Although their metabolic activity is atypical, mature mammalian erythrocytes nevertheless maintain an active glycolytic process and are equipped with an additional incompletely understood oxidative mechanism. These mechanisms provide energy for the maintenance of hemoglobin in an active state and for the transport of substances into and out of the cell, and there is evidence that when these activities cease completely, the cell can never again be made useful. A continuing supply of dextrose, or other nutrient, is necessary to both mechanisms. In other words the cells must be fed during storage. The erythrocyte contains a structural frame necessary, among other things, for the prevention of the escape of the tightly packed intracellular hemoglobin into the plasma. This structure is a selectively permeable network of protein, lipide and polysaccharide, several of its proteins being enzymes. Current concepts suggest that transport through this structure to the interior of the cell is dependent on energy derived from the cell's metabolic processes and is accomplished by specific carriers, the carrier for potassium, *e.g.,* being different than that for sodium. When this transport ceases the cell structure may disintegrate. While maintenance of the metabolism of the cell and maintenance of its structure are actually inseparable processes they sometimes appear to be separable because the measurements used to determine structural integrity may give little information on the metabolic state of the cell, and the reverse is equally true. Many studies of erythrocyte aging have employed only one type of measurement and have thus often yielded data of no meaning for the potential life of the cell after transfusion. To take extreme examples, application of fragility measurements to cells treated with formaldehyde or acrolein will indicate extreme stability of the structure of such cells. The selective permeability of these cells is lost, however, and the pigment is converted entirely to an inactive and useless form. Again, certain types of blood collection provide erythrocytes of unusually high glycolytic activity, suggesting cells of unusual vitality, yet in the presence of this heightened activity the cell membrane is exceedingly fragile.

We have attempted to circumvent some of these difficulties by using routine measurements touching divergent cell properties. Although it is not suggested that these will be found to be the techniques of ultimate choice, we presently employ osmotic fragility studies of

cells previously equilibrated with plasma, the determination of cholinesterase, an enzyme located in or on the cell membrane, and Warburg manometric measurement of the anaerobic glycolytic potential of washed cells suspended in Krebs-Ringer solution. We often find these measurements yielding divergent indications of the state of the cells. Obviously, only studies in which the three types of measurement correlate can be considered to be hopeful.

The problem of feeding the cell during storage obviously can be abetted by slowing the rate of metabolism and reducing the demand for nutrient. This approach has been carried to the point of freezing the blood by several investigators. When one freezes, however, the structural portion of the cell may be disrupted by the transition to and from the crystalline state. This problem has been met by Strumia by freezing at —3°C., by Sloviter by immersing the cell in glycerine prior to freezing and by Luyet by vitrification. In all cooling, however, a problem is presented in that the integrated enzyme systems of metabolism are slowed at different rates, producing a slowly increasing imbalance in intermediate metabolites, and resulting in what Finch has recently called a biochemical lesion. This lesion is partially reversible *in vitro* by equilibration of the cells with fresh plasma and, up to a certain point, completely reversible *in vivo*. But accumulation of metabolites eventually produces a distortion of the cell followed by rupture, either *in vitro* or immediately after transfusion. Cooling and freezing also are known to be detrimental to the lipo-proteins of plasma some of which seem to interact with the erythrocyte membrane. Cooling may in this fashion initiate a nonreversible pattern of deterioration.

Since most of the metabolic enzymes require a proper ionic balance for efficient operation, cell metabolism might be stopped by exchange of essential cations for sodium ions. Work with ion exchange agents has demonstrated either that this is not a tenable concept or that one cannot influence the interior of the cell sufficiently to be of value. A more successful attempt at this approach may be forthcoming trom the work with chelating agents some of which may actually penetrate the erythrocyte membrane. One limitation to this approach may be the dependence of the cell membrane on some of the same cations removed. Cell physiology has shown the dependence of cellular membranes generally on the presence of calcium.

It might be presumed that the colloid osmotic pressure of the plasma proteins would offer important protection in the prevention of the distortion of the cell produced during storage. It can be shown in studies with resuspended cells, however, that certain plasma proteins, present in amounts affording colloid osmotic pressure equivalent to that of plasma offer little protection beyond that provided by isotonic solutions of crystalloid. Other proteins, such as modified globin or a plasma lipoprotein, offer protection completely without relation to their colloid osmotic effect, suggesting an interaction with the cell membrane as the factor determining the value of proteins in cell storage. Production of hypertonicity by the addition of sugars which will not penetrate the red cell has, however, been shown to exert a protective action during storage in the cold.

The very first problem to be met in all blood storage, keeping the blood in a fluid state, may also influence the subsequent durability of the blood cells. Although careful attention to the use of non-wettable surfaces will permit the collection of blood that does not clot rapidly, for the purposes of storage one must resort to some form of anticoagulant. Usually this has meant use of an agent that will bind cationic calcium which is essential in coagulation. At the moment citrate ion remains the agent of choice for this purpose, citrate being less toxic than oxalate and less expensive than heparin. Citrate, however, interacts with many plasma proteins, has an extremely toxic effect on white cells and produces some disturbance of the metabolism of erythrocytes. It would seem desirable to avoid the use of any adulterating agent, if possible. An approach to this has been made in the use of ion-exchange resins which remove the cations rather than binding them. This has resulted in great improvement in the maintenance of the integrity of certain plasma proteins, and of leucocytes and platelets but, as mentioned above, has yielded little or no improvement in erythrocyte aging. Another type of chemical binding agent, ethylene-diamine tetraacetic acid (Versene, Sequestrene) has been employed by Proescher as an anticoagulant and is being extensively studied at present with promise of improvement over citrate.

This brief statement of the problems to be handled in the storage of blood will furnish a background against which we may consider the accomplishment of the past few years in this field. Two studies have been published which suggest real possibility of the extension of the storage life of whole blood.

Smith, Sloviter and associates following the observation that sperm can be preserved for extended periods by freezing in the presence of glycerine, have applied a similar technique to whole blood. Blood frozen rapidly at —79°C. in the presence of an equal quantity of 30% glycerine has been held at this temperature for 42 days, then thawed and transfused with normal survival of those transfused cells which are not lost during the freezing and thawing. This demonstrates that by proper cooling one can sufficiently slow metabolic rates to produce a real extension of storage life. The present limitations of this technique are due to the loss of cells during thawing, which may be extensive in the longer storage periods, and to the difficulty of removing the glycerine before transfusion. This is presently being done by dialysis against graded concentrations of glycerine. Corroboration of this work has not yet appeared in the literature.

Strumia reported an extension of the life of whole blood and a still greater extension of the life of resuspended red cells. This was accomplished by collection of the blood in isotonic neutral citrate solution with careful admixing and refrigeration during the collection. Within 12 hours of collection, lactose, dextrose and citric acid were added to the whole blood, or lactose, dextrose and modified globin were added to red cells in a quantity equivalent to that of the plasma withdrawn. Studies employing the techniques suggested by Strumia have been performed in our laboratory yielding data which appear to corroborate the improvement in aging suggested by him. Resuspension of cells in globin has been studied in at least two other laboratories, however, where lengthened survival *in vivo* has not been found. Careful examination of our data shows that each of the steps suggested are extremely important and that addition of globin may be meaningless unless each step is followed carefully. Both whole blood and resuspended red cells, following the technique of Strumia carefully, have given laboratory evidence of satisfactory preservation for at least three months.

Substitution of 0.3% or 0.6% solutions of Versene in isotonic saline for neutral isotonic citrate solution as an anticoagulant, but otherwise following the technique of Strumia, has yielded laboratory data suggesting improvement in the aging of whole blood as compared to blood collected in ACD solution. The improvement does not appear to approach that obtained when the methods of Strumia are followed precisely.

Search for a plasma protein interacting specifically with the erythrocyte membrane has been extensive. Gibson found evidence of such a protein in Fraction IV-3,4, but his work has never been extended. Recently, in Fraction III-1 such a protein seems to have been found in our laboratory. Identity of the protein has not yet been established but it appears to be a lipo-protein which could readily be made available during routine plasma fractionation.

One major difference between blood in the bottle and blood in the body is the repeated exchange of carbon dioxide for oxygen in the lung. Attempts to oxygenate blood during storage have suggested that this may be a very hopeful technique and may provide the key to correlation of data from studies which have hitherto been baffling. Present effort is being devoted to devising a means of ready continuous oxygenation during storage so that this phenomenon may be accurately evaluated.

In summary, although we cannot begin tomorrow to keep blood for months, techniques may have already been reported that will be shown by corroborative studies to provide for a major extension of our ability to keep both whole blood and resuspended cells. Certainly, the active research in the field gives great promise of advances in our knowledge of blood.

CLINICAL STATUS OF PLASMA FRACTIONS

By Charles A. Janeway, M. D.*

IT IS a pleasure to participate in this symposium. Frequently during the past ten years, the group of investigators to which I have belonged has collaborated with members of the research staff of Sharp and Dohme, as have other groups interested in the blood transfusion problem. I feel sure that the opening of these new laboratories will potentiate the contributions which research workers here, on their own and in collaboration with their colleagues in other laboratories, can make to blood technology and thus to the public health.

Dr. Surgenor has discussed the rationale of plasma fractionation from the standpoint of the chemist concerned with the separation, stabilization, and preservation of each plasma protein in as close to its natural state as possible. I shall discuss these separated proteins from the point of view of the physician who wishes to apply them to the treatment of his patients, of the public health worker, who is interested in the prevention of disease, and of the clinical investigator, who desires to understand the molecular basis of normal bodily functions and their disturbances in disease. For all these purposes, certain requirements must be met. The protein preparations must be of known and reproducible potency, they must be relatively pure and hence specific, they must be available when needed, and, above all, they must be safe. These criteria have been met to a considerable extent in the case of products prepared by the standard alcohol-water method of fractionation; it is our expectation that they will be met even more fully with products prepared by the newer methods, based on interactions with metals. Unfortunately the techniques of clinical investigation are less exact than those of chemistry, and it will probably be many years before the full story of the clinical value and physiological role of any protein fraction can be told. However, during the past decade an impressive body of knowledge about these products has accumulated, and there can be no doubt that they are important therapeutic agents, effective weapons for the control of certain common infectious diseases, and potent tools for clinical and physiological investigation.

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Serum Albumin

The development of serum albumin was predicated on the well-documented assumption that restoration of the volume of circulative plasma was the most urgent need in cases of traumatic shock and that the safest and most effective agent for that purpose would be the natural protein responsible for most of the colloid osmotic pressure of plasma. A great deal of misunderstanding has arisen in the past because of failure to appreciate that packaging of albumin as a 25% solution was for logistic and not for physiologic reasons. The patient in shock from loss of blood or plasma not only loses colloids, but the electrolytes and water in which those colloids are dissolved. Obviously, replacement therapy will be more efficacious if electrolytes and water as well as protein are administered. Serum albumin is effective in restoring lost blood volume in cases of experimental and clinical shock and behaves predictably in terms of its known osmotic and other physico-chemical properties. In view of the safety, convenience, and value of serum albumin as an emergency replacement fluid, in instances of severe injury or blood loss, I hope the day will come when every practicing physician will be able to carry one or two packages in his bag. The fact that the patient receiving serum albumin is safe from the risk of homologous serum hepatitis recommends it particularly as the emergency transfusion fluid of choice.

Serum albumin, with a net charge higher than that of most of the other plasma proteins, is known to interact with and bind many small molecules and ions. Thus, a number of drugs, such as the antimalarials and sulfonamides, fatty acids, and other substances such as thiocyanate ion, are bound in varying degrees to albumin, a fact which determines their transport in the blood and distribution in the body fluids. Our knowledge of the clinical significance of such interactions is rudimentary. The role of serum albumin in the total protein economy of the body, its intermediary metabolism, and its relation to the formation of such tissues as bone matrix are incompletely understood. It seems very likely, however, that as our knowledge is extended, differences between the natural proteins and the foreign colloids under consideration as "plasma expanders" will become increasingly evident.

Specific deficiency of serum albumin occurs frequently in medical and surgical patients. A number of factors may produce it—inade-

quate intake or assimilation of food, loss of albumin in exudates, transudates, or the urine as in the nephrotic syndrome, increased catabolism, or inadequate synthesis to equal the rate of degradation at normal concentrations of serum albumin in the blood. At any given level of circulating albumin, a complex series of equilibria maintain blood volume and govern the distribution of fluids and electrolytes in the body, and their excretion by the kidney. If the level of albumin is low, this homeostatic balance may only be achieved at a price—massive edema. The extent of the participation of the central nervous system, the kidney, and the endocrine system, particularly posterior pituitary and adrenals, in regulation of these equilibria is only beginning to be appreciated. It is not surprising that there is no general agreement on the exact place of albumin in the treatment of hypoproteinemic states. It certainly should be administered where hypoalbuminemia must be quickly repaired, as in preparation of an edematous, hypoproteinemic patient for surgery or in support of such patients during episodes of stress, infection, or in the post-operative period. Patients with gastro-intestinal cancer, ulcerative colitis, severe burns, or adrenal insufficiency frequently require such supportive treatment. Experience has shown that, even though serum albumin may be administered in concentrated solution with little additional fluid or salt, there is a definite limit to the rate at which the readjustments accompanying a rise in serum albumin concentration can be made. This depends on the ability of the circulation to cope with the increase in plasma volume following each injection, an increase which is gradually dissipated through excretion of fluid by the kidneys and by shunting of fluid into the extravascular compartment. In order to raise the serum albumin concentration appreciably, several times as much albumin must be infused, as would be predicted from calculations based on plasma volume. Thus the "albumin space" is much bigger than the measured plasma volume.

Two chronic diseases, cirrhosis of the liver, and the nephrotic syndrome, are regularly associated with a decrease both in the concentration and total amount of circulating albumin. Despite a number of studies on the effects of daily administration for a considerable period in order to relieve the ascites and edema so characteristic of these conditions, observers are not unanimous as to its value or deleterious effects. In early cases of cirrhosis, albumin injections seem to accelerate the onset of the diuresis which usually occurs during a

period of hospital treatment. In advanced cases, there is some risk of rupture of esophageal varices, and the result of albumin administration may only be a parallel rise in colloid osmotic pressure of both blood and ascitic fluid without diuresis. Although daily intravenous albumin injections are well tolerated by most patients with the nephrotic syndrome, and a diuresis occurs in about half of patients so treated, the discomfort of the daily injections, the loss of most of the injected protein in the urine, and the possibility of renal damage from the massive proteinuria had already tended to discourage its use prior to the introduction of corticotropin or cortisone.

Local edema has offered a tempting therapeutic target for concentrated albumin, despite the obvious fact that if edema is localized, a local increase in vascular permeability is its likely cause. Results of albumin administration in instances of cerebral edema, localized edema of the gastrointestinal tract, and inflammatory pulmonary edema have not been uniform.

As a tool in the hands of the clinical investigator, serum albumin has been of great value. As a safe, well-standardized agent for producing a predictable increase in plasma volume it has been used a great deal in studies of the regulation of the circulation. Basic investigations of the hemodynamics of shock and of the role of the brain and kidney in the adjustment of body fluid volume have been made possible. The administration of albumin to patients with cirrhosis of the liver has helped to clarify concepts of the mechanism of ascites. The fact that patients with the nephrotic syndrome lose injected normal albumin almost quantitatively in the urine has strengthened the concept that the disease primarily involves the kidney rather than the plasma proteins. Many interesting metabolic studies which have contributed to our knowledge of protein and calcium metabolism could hardly have been performed without such a safe solution available as a source of parenterally administered protein. Recently serum albumin, labeled with radioactive iodine has been used for plasma volume measurements and as a tool for study of the rate of albumin turnover in normal subjects and patients with cirrhosis of the liver.

S.P.P.S.

Stable plasma protein solution (S.P.P.S.) already described by Dr. Surgenor as the solution remaining after the globulins have been

precipitated from plasma with zinc in the new fractionation process, is a 5% solution of albumins and more soluble globulins in the plasma electrolytes. Theoreticallly, it should be at least as satisfactory as albumin for all uses except those where a concentrated solution is indicated, or the compactness of the albumin package possesses logistic advantages. Clinical trials have been too meager as yet to allow conclusions.

Bi-Metal-Combining Globulin

Fraction IV-7, which contains this metal-combining globulin in high concentration, has not been used as a therapeutic agent because no instances of a specific deficiency of this protein have yet been found. Serving as the normal vehicle for transport of iron in the plasma, it is of great physiological interest and has been employed extensively by a few investigators in studies of iron metabolism.

Serum Gamma Globulin

The gamma globulin fraction, in which almost all the antibodies from large pools of normal human plasma are concentrated 20-25 times, has been used the most extensively of all fractions. Since the demonstration in 1943 that it was a safe, effective agent for the prevention or modification of measles, an estimated over two million doses have been given in this country. Administration of gamma globulin in a small dose to exposed susceptible children so that they develop a mild attack and thus acquire a lasting immunity without serious risk has become standard practice.

With growing appreciation of the potential seriousness of infectious hepatitis, the proof that gamma globulin would prevent or modify their infection in exposed individuals has opened up another large demand for this valuable agent.

Measles and epidemic hepatitis are the only two viral infections of man in which it has been proved that the level of antibody is sufficiently high in the blood of the average normal adult to yield an adequately potent gamma globulin preparation. In the case of chicken pox, mumps, and german measles, diseases which also give a lasting immunity, this is not the case, and it is only from the blood of convalescent donors that an active gamma globulin may be obtained. Mumps convalescent gamma globulin has been used in the treatment

of early mumps in adults to diminish complications, convalescent german measles gamma globulin to protect women exposed in the early stages of pregnancy, when an attack of the disease may produce severe congenital abnormalities in the infant. The collection and preservation of these antibodies, which only are found in human blood in sufficient quantities during convalescence from certain infections, should be a responsibility of any blood program which is conceived in the public interest.

Hyperimmune gamma globulin has only been prepared from the blood of adults who had previously had whooping cough and were given booster doses of pertussis vaccine. It is valuable in the passive protection of infants and for the treatment of severe cases of whooping cough. Hyperimmunization of humans against other diseases, e.g., tetanus or diphtheria, in order to prepare other hyperimmune gamma globulins for clinical use seems worth more extensive exploration than it has yet had.

Recently Stokes has pointed out that active-passive immunization (administration of antibody after exposure to an active infectious agent) is an excellent method for inducing an active immunity with mild or inapparent clinical disease. Widely used by veterinarians, it is the method employed when gamma globulin is used to modify measles in an exposed susceptible child. He and his associates have shown that individuals given gamma globulin during an outbreak of infectious hepatitis in an institution may develop an immunity which far outlasts the duration of passive protection from gamma globulin, even though they may exhibit no overt evidences of infection. They call this passive-active immunization and compare it to the natural phenomenon which occurs in infancy when infections such as measles may be mild or unrecognized if exposure occurs during the period when passive immunity from the mother is waning. These concepts extend the possible uses of gamma globulin to simulate the natural processes of active immunization by exposure to infectious agents in the usual manner.

Recently specific deficiency of gamma globulin, possibly on a congenital basis, has been recognized and described by Bouton. These children are very suspectible to receiving septic infections, cannot produce antibodies in response to antigenic stimuli, but can be protected by regular infections of a moderate dose of gamma globulin every few weeks.

Coagulation Components

Although they comprise a number of different proteins of varying properties and functions, the tendency to interact and liability of the coagulation components has hampered progress in their separation. Products of the new methods have not been available for trial as yet, but should have considerable clinical application, since deficiencies of almost all the major components of the clotting system have been observed, and are usually associated with hemorrhagic phenomena, so that rapid methods for restoring blood coagulability are needed. Only three of these components have been prepared in quantity for clinical use by the alcohol-water method; fibrinogen, antihemophilic globulin, and thrombin.

Fibrinogen has generally been used as Fraction I, of which it comprises 60-70% of the protein, the remainder containing antihemophilic globulin. Fraction I, which must be stored in the dry state and reconstituted just before use, has had three main applications. It was the original agent added to blood to accelerate formation of rouleaux by the red cells and thus their rapid sedimentation, permitting quick separation of red cells and plasma. It has been used for replacement therapy in two types of fibrinogen deficiency—congenital afibrinogenemia and acquired afibrinogenemia, which is occasionally seen in instances of severe post-partum hemorrhage, in which a fibrinolysin presumably derived from the placenta destroys all the patients fibrinogen. In these cases, the injection of large amounts (several grams) of fibrinogen promptly stops the hemorrhage, permitting delivery of the placenta, and is dramatically life-saving.

Thrombin, rather than prothrombin, because of instability of the latter, has been prepared in large amounts as the natural substance most suitable for a local hemostatic agent. To be effective, it must be applied as a solution on some sort of sponge held in place with gentle pressure. Various types of absorbable sponges which can be left in place have been developed—fibrin foam and gelatin foam, for example. Fibrin film, like fibre in foam, made from purified thrombin and fibrinogen, has largely been supplanted by films of plastic.

Antihemophilic globulin received very successful trial as a means of bringing the coagulation time of hemophilic blood down toward the normal range during episodes of hemorrhage or as preparation for

surgical or dental procedures. Actually Fraction I, freshly reconstituted, was used for this purpose. This protein is very unstable, blood losing its potency rapidly on standing. Accordingly, little satisfactory Fraction I has been produced for this purpose, except in the state of Michigan, where it has been prepared from very fresh blood. Hemophilic patients in Michigan carry Fraction I with them in case of emergency, so that, if a hemorrhage begins, they can go to a physician and have him administer it to them.

Further exploration of the problem of separation and purification of the various proteins concerned in clotting is urgently needed now that the newer methods of collection and processing point the way. Many clinical situations exist where specific components might be very valuable therapeutically if they were only available for therapeutic use.

Homologous Serum Hepatitis

Allusion has been made frequently to the safety of these products. There is extensive evidence that serum albumin and gamma globulin have scarcely, if ever, produced hepatitis in recipients, although they have been widely used and are prepared from very large plasma pools. Unfortunately, this is not altogether true of the coagulation components. Fraction I has been shown to contain hepatitis virus in a fair percentage of lots, so that two methods of sterilization for their fraction—ultraviolet irradiation and treatment with 2% nitrogen mustard—have been tried with apparent success, but more extensive documentation is needed. Recently a few preparations of thrombin definitely were shown to be contaminated. However, it sems likely that placental thromboplastin, used for conversion of prothrombin to thrombin, may have been at fault, rather than the thrombin itself.

Summary

Serum albumin and gamma globulin, prepared by the standard alcohol-water method of fractionation, have found a permanent and important place in the treatment and prevention of disease. Their convenience, availability, safety, and standardized potency makes them ideal therapeutic agents from the standpoint of the physician or public health worker and has permitted their widespread use in a series of clinical investigations which have extended our knowledge of human physiology and its disturbances in disease.

Fraction I, as a source both of fibrinogen and of antihemophilic globulin, has demonstrated its great clinical value in the control of hemorrhage due to afibrinogenemia or hemophilia, but cannot be considered an ideal product, due to difficulties with the stability of antihemophilic globulin and to frequent contamination of these lots with hepatitis virus. Thrombin is readily prepared as a valuable natural hemostatic agent for local use in combination with any type of absorbable sponge.

The new methods of blood collection and processing described by another speaker offer an inviting prospect for clinical progress, since they should lead to far better preservation and separation of the labile coagulation components, for which specific clinical indications are obvious. The possibility of collecting, and preserving for use when needed, gamma globulin from individuals convalescent from certain infectious diseases and of preparing gamma globulins from hyperimmunized humans by methods which permit conservation of other valuable blood components from the same donations, such as albumin, fibrinogen, and red cells, deserves more attention *than it has had to date.*

It is my personal belief that we are passing through a revolution in blood technology, to which laboratories such as this will continue to make important contributions, as a result of which the physician will ultimately have at his command specific, standardized, safe therapeutic agents preserved in their natural state for use when needed to correct the physiological disturbances of as many deficiencies of specific blood components as current medical knowledge permits him to recognize. This list is constantly growing. For example, during this current year, as a result of research techniques which are the direct outgrowth of the development of plasma fractionation, our own laboratory has recognized one specific plasma protein deficiency and confirmed the existence of another, both of which were unknown a year ago.

This paper is an attempt to compress an enormous mass of important work by a great many people into a very small space. It is bound to reflect, in many instances, the opinion and probably, the prejudices, of the author—Charles A. Janeway.

FIRST INTERNATIONAL CONGRESS OF HOSPITAL PHARMACISTS TO BE HELD IN BASLE, SWITZERLAND, FROM SEPTEMBER 17 TO SEPTEMBER 19, 1952

IN order to promote exchange of experiences among hospital pharmacists of all countries and to create the possibility of a discussion of mutual problems on a broad basis, the First International Congress for Hospital Pharmacists will take place in Basle, Switzerland, September 17-19, 1952.

The tentative program is as follows:

1. Scientific lectures on a broad scope of subjects of general interest for hospital pharmacists.

2. Lectures on hospital pharmacy administration and organization.

3. Short papers on specific work done by hospital pharmacists (manufacturing, control analysis, clinical-chemical analyses, etc.).

4. Demonstrations of apparatus and instruments for hospital pharmacists.

5. Inspection tours of pharmaceutical manufacturing houses, the hospital pharmacy at Basle, the museum of pharmacy history, etc.

All hospital pharmacists are herewith cordially invited to participate in this meeting and to reserve September 17-19 for the meeting. Reservations should be made as early as possible by writing to Dr. K. Steiger.

For the Organization Committee
of the First International Hospital Pharmacist Congress:

P.-D. DR. K. STEIGER
Kantons-Apotheke, Zürich, Rämstr. 100

SELECTED ABSTRACTS

Rubber Tubing as a Cause of Infusion Thrombophlebitis. Handfield-Jones, R. P. C., and Lewis, H. B. M. *The Lancet 262:*585 (1952). In a preliminary survey 80 infusions were given to a variety of patients. Of this group 38 showed thrombophlebitis, which was defined as thrombosis of more than 1 inch of the vein with redness and edema of the overlying skin. The incidence was found to increase practically linearly with the duration of the infusion.

In an investigation of the causes of this complication of infusion therapy 139 patients were given infusions through sets made up with four different types of rubber. Three of the types were an opaque red rubber, one of which was vulcanized in a different manner by the manufacturer for use in conjunction with this study, and the fourth was a translucent latex tubing. All of this tubing was new and had been thoroughly washed before being sterilized. The red tubing of the type which had been used in the preliminary trial showed an incidence of thrombophlebitis of 44 per cent. The specially vulcanized red tubing showed an incidence of about 8 per cent and the latex tubing showed an incidence of 12 per cent.

The authors concluded that the high incidence of complications was caused by the rubber tubing, primarily. The differences in incidence using the same solutions through the different tubings and the almost direct relation of the incidence to the duration of the infusion brought this conclusion. However, the authors pointed out that other factors may contribute to the incidence of thrombophlebitis. The incidence was higher when glucose or saline was given than when blood alone was given. Since the pH of both glucose and saline is sometimes as low as 4 it has been pointed out that continuous infusion of a solution of such a low pH may contribute to the complications. It was also pointed out that a residue of blood or other debris in tubing which had been used previously may contribute to the condition. However, since the tubing used in the second experiment was all new and had been thoroughly washed this was felt to be a less significant factor.

The authors suggested that further studies should be followed with the objective of determining the biological effects of rubber and of developing standards for the composition of rubber used for therapeutic purposes.

Clinical Evaluation of Methylparafynol. Chevalley, J., Heminway, N., Meyer, G., Frankhauser, R., and McGavack, T. H. *N. Y. St. J. Med. 52*:572 (1952). Methylparafynol (Dormison), the first of a new class of sedative-hypnotics having only carbon, hydrogen and oxygen in the molecule, was administered to a series of 134 patients, mostly chronic. The drug was given in the form of capsules or elixir in daily doses ranging from 100 to 400 mg. for from 2 to 120 days. In most cases it was found that 100 mg. was insufficient to produce sleep. The usual effective dose seemed to be 200 to 300 mg. In patients with pain or mental agitation larger doses were required.

This drug is quickly metabolized in the body. In patients with pain sleep will be produced, even with large doses, for a period of probably 2 or 3 hours. After the drug has been metabolized the patient will respond in the normal way to such outside influences as pain and noise. The short duration of effect has an advantage for the usual patient in that there are no "hang-over" symptoms the following morning.

No side effects were observed or reported by the patients. Urinalyses, blood counts, blood chemistries, and liver function tests were performed before, during, and after the administration of the drug in as many as 37 patients per test. No irregularities of any kind attributable to the action of the drug were observed in these tests.

The drug acted in less than 30 minutes in 67 of 124 patients and in less than an hour in a total of 114 of the 124 patients. In those patients whose duration of sleep was short a second dose of 300 mg. was given. In a few cases 3 doses of 300 mg. each were given at intervals of 2 hours. No contraindications to these repeated doses were noted.

The authors pointed out that methylparafynol probably has its greatest value for patients with simple insomnia and is less effective in those patients with pain or marked mental agitation.

Fundamental Concepts of Developing Dental Caries. Nuckolls, J., Hutton, W. E., Hurst, V., Frisbie, H. E., and Marshall, M. S. *J. Am. Dent. Assoc. 44*:529 (1952). The authors pointed out that far too often a single mechanism has been adopted as the

explanation of the development of dental caries. They felt that a careful evaluation of the many complex factors which have come to light as a result of fundamental research might help to alleviate the confusion attendant upon the various theories of dental caries prevalent today.

Too little attention has been paid to the development of enamel in relation to caries. It has been shown that enamel caries, and also dentin caries, most closely resembles a process whereby there is initially a preferential loss of organic matter. Other studies have shown that the organic enamel matrix may supply, in part, nutrients utilized by bacteria in the initial phases of the disease. It has also been shown that acid decalcification is not identical with caries. Most recent work seems to indicate that simultaneous decalcification and degradation of the enamel matrix are essential to the development of caries. The plaque (accumulation of deposits on the teeth) probably acts as an ecological unit in its contribution to caries. The acid environment resulting from the fermentation of carbohydrates held in the plaque may bring about decalcification of the enamel. The variety of organisms found in the plaque probably also play a part.

It has not been established that certain specific bacteria are the causative agents of caries. Both acidogenic and nonacidogenic organisms have been found associated with carious lesions. Among those which have been thought to be concerned with dental caries are the lactobacilli, the streptococci, the actinomycetes of the plaque, the actinomycetes of the deep lesion and the sulfatase-producing bacteria of Pincus.

The authors pointed out that these concepts of caries development are incomplete and perhaps erroneous in some respects but that they were presented to help broaden the concepts held by many and to stimulate further research.

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